With kind regards

ON CERTAIN POINTS IN CONNEXION WITH

THE EXALTATION AND REDUCTION OF BLOOD COAGULABILITY BY THERAPEUTIC MEASURES

AND IN PARTICULAR ON THE EFFECT PRODUCED UPON THE BLOOD BY THE INGESTION OF CALCIUM CHLORIDE, CALCIUM LACTATE, MAGNESIUM CARBONATE, COW'S MILK, AND OTHER MEDICINAL AGENTS

BY

A. E. WRIGHT, M.D. DUB.,

SOMETIME PROFESSOR OF PATHOLOGY, ARMY MEDICAL SCHOOL, NETLEY; PATHOLOGIST TO ST. MARY'S HOSPITAL;

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W. ERASMUS PARAMORE, M.A., M.B. CANTAB.

(From the Pathological Laboratory, St. Mary's Hospital, London, W.)

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ON CERTAIN POINTS IN CONNEXION WITH THE EXALTATION AND REDUCTION OF BLOOD COAGULABILITY BY THERAPEUTIC MEASURES,

AND IN PARTICULAR ON THE EFFECT PRODUCED UPON THE BLOOD BY THE INGESTION OF CALCIUM CHLORIDE, CALCIUM LACTATE, MAGNESIUM CARBONATE, COW'S MILK, AND OTHER MEDICINAL AGENTS.

FEELING that real advances in therapeutics will be made only when the effects of medicinal agents shall have been followed out on man by the aid of accurate quantitative methods, we have recently—carrying on a line of research already opened up by one of us—made a more detailed study of the accelerating or, as the case may be, retarding action which is exerted by certain medicinal agents upon blood coagulation. We have investigated in particular the accelerating effect which is, as one of us has previously shown, exerted by calcium chloride,[1] and by milk[2] respectively. Further, we have drawn into the scope of this investigation also the lactate of calcium and the carbonate of magnesium. Lastly, we have carried a step further the investigation of the effect exerted upon blood coagulation by the ingestion of decalcifying agents.

Method employed for measuring the content of the blood in calcium and magnesium salts —The method we have employed in the researches reported below is that already described by one of us in conjunction with Lieutenant H. H. G. Knapp, I.M.S., in a paper dealing with the causation and prevention and treatment of the thrombosis which occurs in connexion with typhoid fever.[3] It may briefly be explained here that in the method in question progressive dilutions of a decalcifying

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[1] Brit. Med. Jour., July 29th, 1893, and July 14th, 1894; THE LANCET, Jan. 18th, 1896.

[2] THE LANCET, Dec. 6th, 1902, p. 1531.

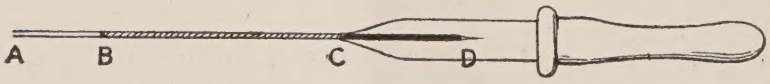
[3] THE LANCET, Dec. 6th, 1902, p. 1531.

solution (oxalate of ammonium) are mixed in a capillary tube with a series of similar volumes of blood. The concentration of the solution required for the complete decalcification is then taken as the measure of the calcium (and magnesium) salts in the blood. Evidence of such complete decalcification of the blood is obtained where it is found that the red corpuscles, instead of becoming engaged in a clot, settle in an even layer at the bottom of the column of fluid.

In the experimental records below the result of the measurements of calcium and magnesium salts in the blood is in each case registered by particularising the concentration of the ammonium oxalate solution [4] which just sufficed to prevent the formation of a coagulum in an equal volume of blood.

Method employed for measuring the coagulation time of the blood.—The method employed for measuring the coagulation time of the blood is the method originally described by one of us modified in certain of its details as described below.

Pattern of coagulation tube employed.—The form of coagulation tube which is depicted below was employed. It consists, as will be seen, of a capillary tube which is divided off



A–B, portion of tube occupied by air; B–C, calibrated portion of the tube which contains the blood; C–D, portion of the tube which contains the mercury which serves to plug the throttled orifice of the tube. On the upper end of the holder is a collapsed rubber teat which maintains the negative pressure and holds the contents of the capillary tube in position when placed upright in water.

by marks into three segments and which is by the aid of sealing-wax luted in an airtight manner into a glass holder. The central segment has been standardised by the aid of mercury and an automatic pipette so as to contain five cubic millimetres in a length of five centimetres. This segment serves for the reception of the blood which is to be tested. Some little distance beyond the fiduciary mark which delimits the upper margin of this segment the capillary tube terminates, as shown in the diagram, in a hair-fine extremity. This upper portion of the tube is filled in with mercury which blocks the hair-fine orifice as soon as the column of blood has taken up its proper position in the tube. Distal to the fiduciary mark which indicates the lower margin of the central segment is a third portion of the tube which is filled in with air so as to prevent any commixture of water with

[4] The equivalent of CaO can from the data obtained be readily computed if it is borne in mind that 142 parts by weight of ammonium oxalate enter into combination with 56 parts by weight of calcium oxide.

the blood when the coagulation tube is immersed in the bath which maintains the proper temperature during the period of observation.

Method of making the pattern of coagulation tube described above.—The first operation in making a coagulation tube is to draw out a piece of ordinary glass tubing into a tube of capillary dimensions. The second is to standardise the tube thus drawn out and to select for use a segment where the bore is of such dimensions as to contain five cubic millimetres of mercury in a length of five centimetres. The details of the operation have already been described in a previous paper in THE LANCET.[5] The third operation is to draw out the capillary tube at some little distance beyond one or other of the fiduciary marks into a hair-fine extremity which shall be pervious to air but impervious to mercury. This is achieved by inserting the capillary tube into a small peep light and drawing it out rapidly after removing it from the flame. The fourth operation is to place a collar of sealing wax round the capillary tube near the neck and to drop the tube—hair-fine extremity uppermost—into, and down, the throat of a glass holder such as is shown in the diagram. By gently warming the throat of the holder the collar of sealing wax is now melted and the capillary tube is fixed in position in an airtight manner. The fifth and last operation is to fix the length of the distal segment of the coagulation tube so that its cubic capacity may be exactly equal to that of the proximal segment. This is achieved as follows. A closely fitting rubber teat having first been fitted to the upper end of the glass holder and a vacuum having been established in the interior the distal end of the coagulation tube is introduced into a reservoir of mercury. By "trial and error" there is now taken up into the tube such a quantum of mercury as will just fill in the proximal segment of the tube. This quantum of mercury having been arrived at, it is by pressure on the teat driven down into the distal segment of the tube, the column of mercury being arrested at the point where its proximal end comes level with the distal calibration mark. The capillary tube is now cut across at the point indicated by the distal end of the mercury column.

Method of measuring the coagulation time of the blood by the aid of the coagulation tubes here in question.—A drop of blood is obtained by pricking the side of the finger near the nail and applying very gentle pressure to the finger pulp. Blood having thus been obtained a coagulation tube which has been furnished with a tightly fitting teat, and which has been primed with the appropriate quantity of mercury, is taken in hand. After the column of mercury has been driven down by pressing on the teat until its upper border comes level with the distal calibration mark, the extremity of the coagulation tube is introduced into the drop of blood on the finger. When the pressure on the teat is relaxed the blood enters the tube. Its inflow is arrested by pressure on the teat as soon as the proximal end of the column of mercury which is in advance of the blood has come level with the proximal calibration mark. When this point has been reached the end of the coagulation tube is withdrawn from the drop of blood on the finger and the mercury is allowed to go home to the extremity of the tube and to engage itself in the hair-fine extremity, preventing further indraught. The column of blood will now be found to have taken up its proper position in the central segment of the tube.

Leaving the rubber teat in position the coagulation tube is now immersed in a water bath at 37° C. placed ready to hand. After the expiration of a minute to a minute and a half the condition of the blood is tested by removing the tube from the water bath and making pressure on the teat in such a manner as to drive out the contained blood, if unclotted, on to a piece of filter paper. When one tube has been tested in this manner a second is taken in hand[6] and is filled in

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[5] Loc. cit.

[6] Where only a single tube is available it will still be possible to measure the coagulation by blowing out on to the filter paper a series of samples of the contents of the tube, returning the tube to the water bath in the intervals.

from a freshly made puncture. A series of three tubes generally suffices for the whole estimation.

Example of the practical working out of the above method.—Seven coagulation tubes are filled in seriatim with blood from the finger of a normal man and are placed in a water bath at 37° C., the times of filling in and testing the tubes being in each case noted.

Tube 1 blown out on to filter paper after					30 sec.			No clot.
Tube 2	,,	,,	,,	,,	45	,,		,,
Tube 3	,,	,,	,,	,,	1 min.			,,
Tube 4	,,	,,	,,	,,	1	,,	15 sec.	,,
Tube 5	,,	,,	,,	,,	1	,,	30 ,,	,,
Tube 6	,,	,,	,,	,,	1	,,	45 ,,	Shred of fibrin.
Tube 7	,,	,,	,,	,,	2	,,		Firm clot.

Evidence of fibrin formation having been obtained after the expiration of 1 minute 45 seconds, while no trace of fibrin was found after 1 minute 30 seconds, the coagulation time of the blood is here taken as 1 minute 37 seconds.

Points to which attention was directed in connexion with the calcium salts and other medicinal agents here experimented with.—We have in the experiments recorded below sought to elicit (*a*) how soon after the ingestion of each medicinal agent the coagulability of the blood is definitely increased? (*b*) what is the maximum acceleration of coagulation which can be achieved by the ingestion of a single dose of the calcium salt or other medicinal agent employed? (*c*) is the increased coagulability of the blood associated with a definite increase in the calcium or, as the case may be, magnesium salts in the blood? and (*d*) how long is the condition of exalted coagulability in each case maintained? These questions are to some extent resolved by the subjoined protocols.

Calcium Chloride.

Observation 1.—H. S. A healthy man. 4 P.M.: Coagulation time, 2 minutes 10 seconds. Complete decalcification with a 1 in 1800 solution of ammonium oxalate. 4.10 P.M.: Four grammes (60 grains) of calcium chloride *cryst.* were administered. 5.10 P.M.: Coagulation time. 35 seconds. A solution of 1 in 800 of ammonium oxalate was required for complete decalcification.

Observation 2.—M. G. A patient suffering from furunculosis. Feb. 20th, 1905:—3.20 P.M.: Coagulation time, 1 minute 35 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 3.35 P.M.: Four grammes of calcium chloride *cryst.* were administered. 5.5 P.M.: Coagulation time, 45 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification.

Observation 3.—De V. K. A healthy man. May 16th, 1905:—2.30 P.M.: Coagulation time, 2 minutes. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 2.45 P.M.: Four grammes of calcium chloride *cryst.* were administered. 3.35 P.M.: Coagulation time, 30 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 17th: Coagulation time, 40 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 18th: Coagulation time, 40 seconds. A solution of 1 in 1500 of ammonium oxalate was required for complete

decalcification. 19th: Coagulation time, 30 seconds. A solution of 1 in 2100 of ammonium oxalate was required for complete decalcification. 20th: Coagulation time, 30 seconds. A solution of 1 in 900 of ammonium oxalate was required for complete decalcification. 23rd: Coagulation time, 45 seconds.

Observation 4.—W. E. P. A healthy man. May 9th, 1905:—4 P.M.: Coagulation time, 1 minute 50 seconds. A solution of 1 in 1050 of ammonium oxalate was required for complete decalcification. 4.15 P.M.: Four grammes of calcium chloride were ingested. 5.15 P.M.: Coagulation time, 55 seconds. A solution of 1 in 750 of ammonium oxalate was required for complete decalcification. 10th: Coagulation time, 1 minute. A solution of 1 in 750 of ammonium oxalate was required for complete decalcification. 11th: Coagulation time, 1 minute. A solution of 1 in 600 of ammonium oxalate was required for complete decalcification. 12th: Coagulation time, 1 minute. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 13th: Coagulation time, 1 minute. A solution of 1 in 1200 ammonium oxalate was required for complete decalcification. 15th: Coagulation time, 1 minute 30 seconds. A dilution of 1 in 1800 of ammonium oxalate was required for complete decalcification.

Observation 5.—X. Y. A patient who was suffering from œdema of the eyelids and lips and aggravated urticaria. July 5th, 1905:—2 P.M.: Coagulation time, 2 minutes 15 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 3.50 P.M.: Four grammes of calcium chloride were administered. 5.55 P.M.: Coagulation time, 45 seconds. A solution of 1 in 750 was required for decalcification. 13th: The patient reported that the urticaria had completely disappeared. Coagulation time, 48 seconds. A solution of 1 in 900 was required for decalcification.

Observation 6.—A. E. W. A healthy man who had as a boy frequently been the subject of aggravated giant urticaria on the ingestion of decalcifying agents (acid fruits, &c.). Feb. 30th, 1905:—1.30 P.M.: Coagulation time, 1 minute 45 seconds. A solution of 1 in 1500 of ammonium oxalate was required for complete decalcification. 1.45 P.M.: Four grammes of calcium chloride were ingested. 2.45 P.M.: Coagulation time, 1 minute 30 seconds. A solution of 1 in 1500 of ammonium oxalate was required for complete decalcification.

Observation 7.—A. E. W. (*vide* Observation 6 *supra*). May 12th, 1905:—2.30 P.M.: Coagulation time, 2 minutes 10 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 2.50 P.M.: Four grammes of calcium chloride were ingested. 3.50 P.M.: Coagulation time, 1 minute 50 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification.

Summary of Results obtained with Calcium Chloride.

(*a*) *Time required for the achievement of increased blood coagulability.*—The observations show in a very concordant manner that the full accelerating effect of calcium chloride is achieved within the first hour after its administration.

(*b*) *Extent to which the coagulability of the blood is increased by the administration of calcium chloride.*—The data obtained in this series of observations are as follows. With a single dose of four grammes (60 grains) of calcium chloride *cryst.* the coagulation time of the blood was reduced—

In Observation 1 from 2 minutes 10 seconds to 35 seconds—i.e., in the ratio of 1 to $\frac{1}{4}$.

In Observation 2 from 1 minute 35 seconds to 45 seconds—i.e., n the ratio of 1 to $\frac{1}{2}$.

In Observation 3 from 2 minutes to 30 seconds—i.e., in the ratio of 1 to $\frac{1}{4}$.

In Observation 4 from 1 minute 50 seconds to 55 seconds—i.e., in the ratio of 1 to $\frac{1}{2}$.

In Observation 5 from 2 minutes 15 seconds to 45 seconds—i.e., in the ratio of 1 to $\frac{1}{3}$.

In Observation 6 from 1 minute 45 seconds to 1 minute 30 seconds—i.e., in the ratio of 1 to $\frac{6}{7}$.

In Observation 7 from 2 minutes 10 seconds to 1 minute 50 seconds—i.e., 1 to $\frac{3}{4}$.

(*c*) *Absorption of calcium salts into the blood.*—In Observations 1, 3, and 5 sati-factory evidence was obtained of the entrance of calcium salts into the blood. In the second of these cases, where the observations were extended over a week, the lime salts in the blood were seen to diminish contemporaneously with the return of coagulability to the normal.

(*d*) *The period during which the effect of the single dose of calcium was maintained.*—In Observations 3, 4, and 5 where this point was investigated the increased blood coagulability was found to be maintained in Observation 3 for five days, in Observation 4 for eight days, and in Observation 5 for eight days.

Comment.—It is brought out in the results tabulated under (*b*) *supra* that there are as between different individuals conspicuous differences in their capacity of responding to calcium chloride. These differences may, in view of the facts summarised under (*c*); further in view of the fact that results altogether similar to those recorded in Observations 6 and 7 in connexion with A. E. W. had previously been obtained upon him on quite a number of different occasions; and lastly, in view of the case of a bleeder[7] whose blood coagulation was quite uninfluenced by large doses of calcium chloride given by the mouth, while it was conspicuously increased by hypodermic injection of a suitable calcium salt; be referred to constitutional differences in the matter of the absorption of calcium chloride. A constitutional incapacity, or partial incapacity, of this nature may perhaps underlie the "idiosyncrasy" of certain persons to suffer from those forms of urticaria which one of us has denoted "decalcification urticarias."[8] We might quite reasonably expect that the absorption into the blood of decalcifying agents (soap from soap enemas; oxalic acid from rhubarb; citric, tartaric, and

[7] It is to be noted that a deficient power of absorbing calcium salts is not by any means a common feature in hæmophilia. One of us, in recommending the employment of calcium chloride in hæmophilic hæmorrhages, has given examples of the notable acceleration of coagulation time which may generally be obtained in these patients by the exhibition of calcium chloride. (Brit. Med. Jour., July 14th, 1894; THE LANCET, Jan. 18th, 1896, p. 153.)

[8] Transactions of the Pathological Society, vol. li., part 3, 1900.

malic acid from sour fruits, fruit juices, and acid wines) would induce a condition of diminished blood coagulability, and in association with this "serous hæmorrhages"[9] in persons who happened to be unable to maintain their store of calcium salts at a high level, or to replenish it rapidly when encroached upon. It is interesting in this connexion to bring into relation with the defective power of absorption for calcium chloride demonstrated to exist in A. E. W. the fact that he had suffered for a period of years during boyhood from aggravated giant urticaria whenever any decalcifying agent was ingested. Again, it is perhaps deserving of passing mention that in his case, contrary to what was shown[10] by him to obtain in connexion with those forms of urticaria which are superinduced by serum injections, the exhibition of calcium chloride neither warded off nor relieved a severe attack of urticaria engendered by the injection of serum.

Whatever may be the view taken with regard to these suggested explanations it will not be questioned that it became desirable, in view of the facts disclosed above, to see whether an effective substitute could be obtained for calcium chloride for employment in those cases where this latter drug by reason of its non-absorption fails to increase the coagulability of the blood.

We selected for purposes of study the lactate of calcium, a salt which had already for some time past been employed by one of us with very satisfactory results in the control of actual and serous hæmorrhage. This salt recommends itself for use, firstly, by the fact that it is devoid of unpleasant taste, sufficiently soluble (about 1 in 10) in water, and suitable for administration in the form of powders, and, secondly, by the fact that the salts of organic acids, and more particularly of lactic acid, are known to be readily oxidised in the system, with the result that their bases are placed more fully at the disposal of the organism than these would be the case when the corresponding mineral acid salts are exhibited.

Calcium Lactate.

Observation 1.—M. G. A patient suffering from furunculosis.[11] April 18th, 1905:—3.10 P.M.: Coagulation time, 1 minute 50 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 3.30 P.M.: Four grammes of calcium lactate were administered. 4.20 P.M.: Coagulation time, 45 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 6 P.M.: Coagulation time, 30 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification.

Observation 2.—De V. K. A healthy man.[12] Feb. 20th, 1905:—5.10 P.M.: Coagulation time, 2 minutes. A solution of 1 in 1500 of

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[9] The Lancet, Sept. 19th, 1896, p. 807.

[10] The Lancet, Jan. 18th, 1896; British Journal of Dermatology, vol. viii., No. 89.

[11] A previous observation had been made upon this patient with calcium chloride (*vide* under Calcium Chloride, Observation 2).

[12] An observation was subsequently made upon this "patient" with calcium chloride (*vide* under Calcium Chloride, Observation 3).

oxalate of ammonium was required for complete decalcification. 5.15 P.M.: Four grammes of calcium lactate were ingested. 6 P.M.: Coagulation time, 50 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 9.15 P.M.: Coagulation time, 40 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 21st: Coagulation time, 50 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 22nd: Coagulation time, 45 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 23rd: Coagulation time, 50 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 24th: Coagulation time, 37 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 25th: Coagulation time, 45 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 26th: Coagulation time, 45 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for comple decalcification. 27th: Coagulation time, 48 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. March 6th: Coagulation time, 55 seconds. A solution of 1 in 1000 was required for complete decalcification.

Observation 3.—F. M. The patient was suffering from phthisis. Feb. 7th, 1905:—2.30 P.M.: Coagulation time, 1 minute 50 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 8th: 2 P.M.: Coagulation time, 1 minute 55 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 2.15 P.M.: Four grammes of calcium lactate were administered. 3 P.M.: Coagulation time, 22 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 9th: Coagulation time, 1 minute 35 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification.

Observation 4.—A healthy man. Feb. 6th, 1905:—2 P.M.: Coagulation time, 1 minute 50 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 2.20 P.M.: Four grammes of calcium lactate were administered. 2.30 P.M.: Coagulation time, 1 minute 50 seconds. 2.40 P.M.: Coagulation time, 1 minute 20 seconds. 3.50 P.M.: Coagulation time, 25 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 7th: Coagulation time, 1 minute 25 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 10th: Coagulation time, 45 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification.

Observation 5.—A healthy man. Feb. 21st, 1905:—3 P.M.: Coagulation time, 1 minute 40 seconds. A solution of 1 in 1800 of ammonium oxalate was required for complete decalcification. 3.15 P.M.: Four grammes of calcium lactate were administered. 4 P.M.: Coagulation time, 45 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 22nd: Coagulation time, 35 seconds. 24th: Coagulation time, 45 seconds. March 1st: Coagulation time, 1 minute 20 seconds.

Observation 6.—A. E. W. A healthy man.[13] May 15th, 1905:—2.45 P.M.: Coagulation time, 2 minutes 5 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 3 P.M.: Four grammes of calcium lactate were ingested. 4 P.M.: Coagulation time, 1 minute 5 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification.

Observation 7.—W. E. P. A healthy man.[14] Feb. 3rd, 1905:—2 P.M.: Coagulation time, 1 minute 45 seconds. A solution of 1 in 1800 of

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[13] Two previous observations made upon this man with calcium chloride are recorded above.

[14] A previous observation made upon this man with calcium chloride is recorded above.

oxalate of ammonium was required for complete decalcification. 2.15 P.M.: Four grammes of calcium lactate were ingested. 3 P.M.: Coagulation time, 1 minute 15 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 6 P.M.: Coagulation time, 1 minute 20 seconds. 9 P.M.: Coagulation time, 1 minute 20 seconds. 4th: Coagulation time, 1 minute 35 seconds. A solution of 1 in 2000 of oxalate of ammonium was required for complete decalcification.

Summary of Results obtained with Calcium Lactate.

(*a*) *Time required for the achievement of increased blood coagulability.*—As in the case of calcium chloride the effect of the drug is very rapidly manifested. Increased coagulability may, as shown in Observation 4, be registered within 20 minutes of the administration of the drug. The full effect is in practically every case achieved within the course of three-quarters of an hour.

(*b*) *The extent to which the coagulability of the blood is increased.*—With a single dose of four grammes (60 grains) of calcium lactate the coagulation time of the blood was reduced—

In Observation 1 from 1 minute 50 seconds to 30 seconds—i.e., in the ratio of 1 to $\frac{1}{4}$.

In Observation 2 from 2 minutes to 40 seconds—i.e., in the ratio of 1 to $\frac{1}{3}$.

In Observation 3 from 1 minute 50 seconds to 22 seconds—i.e., in the ratio of 1 to $\frac{1}{5}$.

In Observation 4 from 1 minute 50 seconds to 25 seconds—i.e., in the ratio of 1 to $\frac{1}{5}$.

In Observation 5 from 1 minute 40 seconds to 45 seconds—i.e., in the ratio of 1 to $\frac{1}{3}$.

In Observation 6 from 2 minutes 5 seconds to 1 minute 5 seconds—i.e., in the ratio of 1 to $\frac{1}{2}$.

In Observation 7 from 1 minute 45 seconds to 1 minute 15 seconds—i.e., in the ration of 1 to $\frac{5}{7}$.

(*c*) *Absorption of calcium salts into the blood.*—In four out of the seven observations satisfactory evidence of the dependence of the increased coagulability upon the absorption of calcium salts was obtained (Observations 1, 2, 4, and 7).

(*d*) *Period during which the effect of a single dose of calcium lactate is maintained.*—This question was investigated only in connexion with Observations 2 and 4. In the former case the effect was maintained for a minimum of 17 days and in the latter for a minimum of four days.

Comment.—The data set forth above under (*b*) show very clearly that the acceleration of blood coagulability achieved by the ingestion of four grammes of calcium lactate is, if anything, greater than that achieved with the same dose of calcium chloride. It would seem probable from a comparison

of the data set out under (*c*) with the corresponding data obtained with calcium chloride that this more satisfactory result is referable to a readier absorption of the lactate. With regard to the question as to whether the difficulties in connexion with the absorption of lime are solved by the substitution of the lactate for the chloride it will be obvious that no certain conclusions could be arrived at from the limited data as set forth above. At the most these data suggest that the lactate is in the case of one of us (W. E. P.) less well resorbed than the chloride, while in the case of the other of us (A. E. W.) the contrary appears to be the case. We have, however, in the case of the hæmophilic patient already referred to conclusive evidence that the difficulty in connexion with the resorption of calcium is not disposed of by the substitution of the lactate for the chloride. Reserving the further exposition of this case for a subsequent section of this paper we may here pass on to consider a third series of protocols relating to the effect exerted upon blood coagulability by the ingestion of magnesium carbonate.

Magnesium Carbonate.

Observation 1.—A. E. W. A healthy man. June 20th, 1905: Coagulation time, 2 minutes. 4.30 P.M.: Four grammes of magnesium carbonate were ingested. 21st: Coagulation time, 45 seconds. 22nd: Coagulation time, 1 minute 15 seconds. 23rd: Coagulation time, 1 minute 15 seconds.

Observation 2.—W. E. P. A healthy man. June 19th, 1905:—12.30 P.M.: Coagulation time, 1 minute 5 seconds. Coagulation averted when the blood was mixed with an equal volume of a 1 in 1800 solution of oxalate of ammonium. 3.35 P.M.: Four grammes of magnesium carbonate were ingested. 4.45 P.M.: Coagulation time, 30 seconds. 20th: Coagulation time, 28 seconds. Coagulation not averted until the blood was mixed with an equal volume of a 1 in 600 solution of oxalate of ammonium. 21st: Coagulation time, 25 seconds. Coagulation not averted until the blood was mixed with an equal volume of a 1 in 900 solution of oxalate of ammonium. 22nd: Coagulation time, 33 seconds. Coagulation not averted until the blood was mixed with an equal volume of a 1 in 600 oxalate of ammonium solution. 23rd: Coagulation time, 42 seconds. Coagulation averted when the blood was mixed with a 1 in 1200 solution of oxalate of ammonium.

Observation 3.—R. A healthy man. June 19th, 1905:—4.30 P.M.: Coagulation time, 40 seconds. Coagulation averted when the blood was mixed with an equal volume of a solution of 1 in 2400 of oxalate of ammonium. 5 P.M.: Four grammes of magnesium carbonate were ingested. 7 P.M.: Coagulation time, 1 minute 10 seconds. Coagulation only incompletely averted when the blood was mixed with an equal volume of a solution of 1 in 2400 of oxalate of ammonium. 20th: Coagulation time, 25 seconds. Coagulation not averted till the blood was mixed with an equal volume of a 1 in 1200 oxalate of ammonium solution. 21st: Coagulation time, 50 seconds. A 1 in 1500 solution was the minimum concentration of oxalate of ammonium which averted coagulation. 22nd: Coagulation time, 33 seconds. A 1 in 1500 solution of ammonium oxalate was the minimum dilution which sufficed to avert blood coagulation. 23rd: Coagulation time, 25 seconds. A 1 in 1200 solution of ammonium oxalate was the minimum dilution which sufficed to avert coagulation. 24th: Coagulation time, 30 seconds.

Observation 4.—F. A healthy man. June 19th, 1905:—1.5 P.M.: Coagulation time, 35 seconds. Coagulation averted when the blood

was mixed with an equal volume of a 1 in 1800 solution of oxalate of ammonium. 4.15 P.M.: Four grammes of magnesium carbonate were ingested. 6.30 P.M.: Coagulation time, 35 seconds. Coagulation was averted when the blood was mixed with an equal volume of a 1 in 2500 solution of oxalate of ammonium. 20th: Coagulation time, 33 seconds. Coagulation was not averted until the blood had been mixed with an equal volume of a 1 in 1200 oxalate of ammonium solution. 22nd: Coagulation time, 33 seconds. Coagulation was averted when the blood was mixed with an equal volume of a 1 in 1500 oxalate of ammonium solution.

Observation 5.—C. A patient suffering from cystitis. June 13th. 1905:—4 P.M.: Coagulation time, 1 minute 40 seconds. A 1 in 900 oxalate of ammonium solution was the minimum dilution which averted blood coagulation. 4.20 P.M.: Four grammes of magnesium carbonate were administered. 5.30 P.M.: Coagulation time, 45 seconds. Coagulation was not averted until the blood had been mixed with an equal volume of a 1 in 750 solution of oxalate of ammonium.

Summary and Comment.

In the case of the experiments reported above which were conducted by administering in each case 60 grains of magnesium carbonate the blood coagulation time was accelerated—

In Observation 1 from 2 minutes to 45 seconds—i.e., in the ratio of 1 to $\frac{3}{4}$.

In Observation 2 from 1 minute 5 seconds to 25 seconds—i.e., in the ratio of 1 to $\frac{5}{13}$.

In Observation 3 from 40 seconds to 25 seconds—i.e., in the ratio o 1 to $\frac{5}{8}$.

In Observation 5 from 1 minute 40 seconds to 45 seconds—i.e., in the ratio of 1 to $\frac{1}{2}$.

In Observation 4 the blood coagulation time, which was already very short, remained at 35 seconds.

In the case of two of these observations the acceleration of blood coagulation time was registered in an hour from the time of administration of the drug. In Observations 2, 3, 4, and 5 distinct evidence was obtained of an absorption of magnesium salts into the blood.

The evidence furnished above that magnesium salts exert when ingested an effect which is quite comparable to that exerted by calcium salts is exactly what might have been expected in view (*a*) of the close chemical affinities which obtain as between magnesium and calcium, and (*b*) of the original experiments of Arthus and Pagès, which showed that magnesium salts induced coagulation in oxalated blood *in vitro* in exactly the same manner as calcium salts. The disclosure of the effect which magnesium salts exert on blood coagulation is of therapeutic interest as explaining the *rationale* of the employment of magnesium carbonate in the treatment of urticaria and the special efficacy of the drug —as one of us has learned by experience on his own person— in the treatment of that form of urticaria which supervenes upon the ingestion of decalcifying agents. The specific remedial action here exerted is obviously not, as the pathology of a pre-scientific age assumed, the result of a neutrali-

sation of acid properties in the blood, but the result of the replenishment of the blood with the salts which render the plasma coagulable and viscid.

From the study of the effect produced upon the blood by the ingestion of calcium and magnesium salts we pass on to study the effect which is exerted upon the blood coagulation by the ingestion of cow's milk. The line of thought which prompts to this inquiry will immediately suggest itself to the reader who is familiar with the observations made by one of us in conjunction with Knapp,[15] which show that the thrombosis which so frequently occurs in connexion with convalescence from typhoid fever almost certainly stands in relation with an excess of calcium salts furnished to the typhoid fever patient in the exclusively milk dietary which is so generally imposed upon him.

Cow's Milk.

Observation 1. - H. K. A healthy medical student. May 15th, 1905:—Coagulation time 2 minutes 22 seconds. A solution of 1 in 1800 of oxalate of ammonium added to the blood in equal volumes effected complete decalcification. Two pints of milk a day were now added to the dietary which remained in other respects unaltered. 17th: Coagulation time, 45 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 18th: Coagulation time, 45 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 20th: Coagulation time, 30 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. 22nd: Coagulation time, 50 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. 23rd: Coagulation time, 1 minute. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. 24th: Coagulation time, 30 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 25th: Coagulation time, 20 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 26th: Coagulation time, 45 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification.

Observation 2.—B. A healthy medical student. May 17th, 1905:—Coagulation time, 1 minute 25 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. Two pints of milk a day were now added to the dietary, which remained the same in other respects. 18th: Coagulation time, 45 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 19th: Coagulation time, 45 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium. 20th: Coagulation time, 1 minute. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium. 23rd: Coagulation time, 40 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium. 24th: Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium. 25th: Coagulation time, 35 seconds. Complete decalcification with a dilution of 1 in 1050 of oxalate of ammonium. 27th: Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 750 of oxalate of ammonium. 29th: Milk left off. 31st: Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium. June 6th: Coagulation time, 33 seconds. Complete decalcification with a dilution of 1 in 750 of oxalate of ammonium. 7th: Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 750 of oxalate of ammonium. 10th: Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium.

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[15] The Lancet, Dec. 6th, 1902, p. 1531

Observation 3.—**L.** A patient suffering from pleurisy with effusion. Feb. 10th, 1905: Coagulation time, 1 minute 20 seconds. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium. Two pints of milk were now added to the patient's dietary. 11th: Coagulation time, 1 minute 40 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 12th: Coagulation time, 55 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 13th: Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 14th: Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 200 of oxalate of ammonium. 15th: Coagulation time, 40 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 16th: Coagulation time, 45 seconds. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium.

In addition to these observations, where the blood was examined both before and after the addition of milk to the dietary, we have made also a certain number of observations upon adults who happened to be taking a considerable quantity of milk and also upon infants. The data obtained in this manner are tabulated below.

Serial number of observation.	Description of patient.	Particulars with respect to amount of milk in dietary.	Minimum concentration of oxalate of ammonium solution required for complete decalcification of an equal volume of blood.	Coagulation time.
				Seconds.
4	Phthisical patient.	1 to 1½ pints of milk daily.	1 in 1500	30
5	,,	,,	1 in 800	35
6	,,	,,	1 in 800	50
7	,,	,,	1 in 800	20
8	Healthy man.	1 pint of milk on 4 preceding days.	1 in 800	30
9	,,	1 to 2 pints of milk regularly.	1 in 1500	35
10	,,	1½ pints of milk regularly.	1 in 1500	55
11	,,	1 to 2 pints of milk regularly.	1 in 1200	50
12	Infant aged 6 months.	Dietary of cow's milk.	1 in 600	25
13	Infant aged 4 months.	Dietary of cow's milk and barley water.	1 in 750	25
14	Infant aged 4 months.	Fed on human milk supplemented by cow's milk.	1 in 1200	37
15	Infant aged 6 weeks.	Fed on human milk.	1 in 750	30
16	Infant aged 19 months.	½ pint of cow's milk daily.	1 in 900	25
17	Infant aged 2 months.	Fed on human milk.	1 in 600	25

Summary of Results and Comment.

It will be seen that the above observations—which are in close agreement with those made by one of us in conjunction with Knapp on typhoid fever convalescents—show in a consistent manner that the coagulability of the blood is increased by the ingestion of milk, and that this increased coagulability is associated with the presence of large quantities of calcium and magnesium salts in the blood. It follows that milk is much more than a food-stuff. It is also in an eminent degree a medicinal agent. As such it may exert, according to circumstances, either a beneficial or a prejudicial effect. While advantage may accrue from the prescription of milk in connexion with hæmorrhage, aneurysm, physiological albuminuria, and the œdema of Bright's disease, it is practically certain that in many other cases the medicinal effect of milk is exerted to the prejudice of the patient. The importance of this aspect of the matter will not need to be enforced upon anyone who will let it come home to him that every patient—or rather let us say, every adult patient—who is placed on a dietary of milk is thereby brought into a condition which predisposes to thrombosis. We would throw it out as a suggestion that it would be profitable to make a systematic inquiry into the frequency with which thrombosis supervenes in hospital patients placed on a dietary of milk.

We pass now to the consideration of certain final points relating to the therapeutic exploitation of the medicinal agents which are available for increasing and diminishing the coagulability of the blood.

Dosage to be employed where calcium or, as the case may be, magnesium salts are exhibited for the purpose of achieving as rapidly as possible a considerable exaltation of blood coagulability.—The experiments which have been detailed above make it clear that a rapid increase of blood coagulability such as is desired for the arrest of actual or serous hæmorrhage can, unless in the case where we are dealing with a person who is defective with respect to his power of absorbing calcium salts, be achieved by the administration of a single 60-grain dose of either calcium lactate or, as the case may be, calcium chloride.

Dosage to be employed where calcium salts are to be exploited for the purpose of maintaining a permanently high level of blood coagulability.—Success in maintaining the blood coagulability at a high level involves adjusting successive doses of calcium salts in such a manner as to avoid introducing into the blood such excess of these salts as would effect a retardation of blood coagulation time.

Observation.—R. Healthy man. Feb. 23rd, 1905: Coagulation time, 1 minute 35 seconds. Complete decalcification with a dilution of

1 in 1800 of oxalate of ammonium. 15 grains of calcium lactate were given three times a day. 24th: Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 1500 of oxalate of ammonium. 25th: Coagulation time, 35 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 27th: Coagulation time, 35 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 28th: Coagulation time, 25 seconds. Complete decalcification with a dilution of 1 in 1500 of oxalate of ammonium. March 1st: Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 1000 of oxalate of ammonium. 2nd: Coagulation time, 47 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. The drug was discontinued on the 3rd. 6th: Coagulation time, 55 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium.

The next protocol we owe to our fellow-worker, Dr. George W. Ross. Dr. Ross kindly undertook to investigate here in association with the primary question at issue also the subsidiary question as to whether the presence of an excess of calcium salts in the blood would betray itself on examination of the patient's serum. The protocol refers to a case of aneurysm of the arch of the aorta under the care of Dr. E. C. Beale.

First period, April 12th to 16th, 1905.—In this period, which preceded the administration of calcium salts, the patient's blood was tested on two occasions. The results of the blood examinations were as follows:—April 12th: Blood coagulation time, 1 minute 50 seconds. Concentration of oxalate of ammonium solution required for complete decalcification, 1 in 1350. 16th: Blood coagulation time, 1 minute 50 seconds. Concentration of ammonium oxalate required for complete decalcification, 1 in 1350.

Second period, April 18th to 25th, 1905.—During this period 20 grains of calcium lactate were administered three times a day. The results of the blood examinations made during this period were as follows:—April 19th: Blood coagulation time, 1 minute 20 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 1200. 21st: Blood coagulation time, 1 minute 25 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 1000. 23rd: Blood coagulation time, 1 minute 35 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 800. 25th: Coagulation time, 1 minute 50 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 1000.

The patient's serum was now tested for calcium salts on the idea that these would when present in excess in the blood remain in solution in the serum instead of disappearing, as is normally the case, in the course of the chemical changes associated with blood coagulation. It was found in accordance with what was expected that the presence of calcium salts could be demonstrated in the patient's serum.[16]

Third period, May 1st to 13th, 1905. After an interval of four days, during which no calcium salts were exhibited, 20 grains of calcium lactate were again administered three times a day. The results of the blood examinations made during this period were as follows. May 2nd: Blood coagulation time, 1 minute 20 seconds. 4th: Blood coagulation time, 1 minute 15 seconds. 6th: Blood coagulation time, 1 minute 20 seconds. 8th: Blood coagulation time, 1 minute 35 seconds.

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[16] The method employed for testing for the presence of calcium salts in the serum was as follows. Two series of progressive dilutions of oxalate of ammonium were made up, the menstruum employed for the dilution being, in the one case, the patient's serum and, in the other case, a solution of chemically pure sodium chloride. The calcium salts of the observer's blood were now measured in duplicate, first with the

10th: Blood coagulation time, 1 minute 50 seconds. 12th: Blood coagulation time, 1 minute 50 seconds.

Fourth period, May 14th to June 24th, 1905. During this period ten grains of calcium lactate were administered three times a day. The following results were obtained. May 26th: Blood coagulation time, 1 minute. 30th: Blood coagulation time, 1 minute 15 seconds. June 3rd: Blood coagulation time, 1 minute 10 seconds. 10th: Blood coagulation time, 1 minute 20 seconds. 24th: Blood coagulation time, 1 minute 20 seconds.

On the possibility of introducing calcium salts into the blood by hypodermic injection in the case where they are not absorbed when given by the mouth.—Our personal experience of hypodermic injection of calcium salts in man is limited to a single case—that of a bleeder before referred to who appears to be incapable of absorbing any calcium salts administered by the mouth. The particulars given below represent the unfortunately in some respects incomplete observations which were made (many of these observations were kindly made for us by Dr. J. B. Nias) upon this bleeder on four successive occasions when he presented himself, as is his wont, at this laboratory to see whether anything could be done for the relief of the hæmorrhages which, in his case, occur on each occasion from roots of the upper teeth.

Observation 1.—H. G., a man, suffering from hæmophilia. Feb. 8th, 3 P.M.: Coagulation time, 2 minutes 15 seconds. 3.10 P.M.: 4 grammes of calcium lactate were given by the mouth. 3.50 P.M.: Coagulation

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one and then with the other series of progressive dilutions. The results obtained are exhibited in tabular form below:—

Table showing the Concentrations of Oxalate of Ammonium which when Dissolved in Serum and Salt Solution Respectively Effected the Complete Decalcification of or (as the Case may be) just Failed Completely to Decalcify a Test Blood.

Date of examination.	Oxalate of ammonium dissolved in the patient's serum.		Oxalate of ammonium dissolved in physiological salt solution.	
	Dilution which effected complete decalcification of an equal volume of the observer's blood.	Dilution which failed to effect complete decalcification of an equal volume of the observer's blood.	Dilution which effected complete decalcification of an equal volume of the observer's blood.	Dilution which failed to effect complete decalcification of an equal volume of the observer's blood.
25/4/05	1 in 600.	1 in 800.	1 in 1350.	1 in 1500.

It will be seen that more concentrated solutions of oxalate of ammonium in the patient's serum were required to effect the same decalcifying effect which was exerted by less concentrated solutions of oxalate of ammonium in a menstruum of sodium chloride. The difference must be ascribed to the presence of calcium salts in the patient's serum.

time, 2 minutes 15 seconds. No effect was exerted upon the hæmorrhage.

Observation 2.—Feb 17th, 2.30 P.M.: Coagulation time, 2 minutes 50 seconds. 2.40 P.M.: 4 grammes of calcium lactate were administered 3.25 P.M.: Coagulation time, 2 minutes 45 seconds. No effect was exerted on the hæmorrhage.

Observation 3.—Feb. 24th, 4 P.M.: Coagulation time, 2 minutes 50 seconds 4.10 P.M.: Subcutaneous injection of 0·5 gramme of calcium lactate in 10 cubic centimetres of water. 4.55 P.M.: Coagulation times, 2 minute 10 seconds. No marked effect was exerted on the hæmorrhage.

Observation 4.—March 3rd, 2.10 P.M.: Coagulation time, 2 minutes 5 seconds. There was continuous hæmorrhage from the gums. 2.30: Hypodermic injection of 0·6 gramme of calcium lactate. 2.45: Hæmorrhage from the gums has ceased. 3.30 P.M.: Coagulation time, 40 seconds. 4.30 P.M.: Coagulation time, 35 seconds. March 6th: Coagulation time, 50 seconds. 16th: Coagulation time, 2 minutes 10 seconds.

In publishing this case we would venture to add a warning against employing calcium chloride for hypodermic injection, and we would suggest that if the hypodermic injection of lactate of calcium is resorted to the maximum concentration of the drug employed should be a 1 in 20 solution.

On the therapeutic measures to be employed for diminishing the coagulability of the blood and for maintaining a condition of diminished coagulability.—It was pointed out a good many years ago by one of us that it was possible to decalcify the blood and diminish blood coagulability by the administration of citric acid. The practical importance of this therapeutic measure in connexion with the treatment of thrombosis was further pointed out by one of us in conjunction with Knapp in a paper already referred to. We come back upon the subject here to supplement what was said in the paper last referred to in the light of experience recently gained in connexion with the examination of certain cases of hæmorrhage into the vitreous which were under the treatment of Mr. Leslie Paton in the out-patient department of this hospital. After it had been ascertained by a blood examination that the coagulation times of these three patients were respectively 1 minute 10 seconds, 50 seconds, and 1 minute 35 seconds, citric acid was in each case prescribed with intent to reduce the blood coagulability and to keep it throughout the course of the treatment at a low level. In each case the former but not the latter object was achieved. In the first case the coagulation time was reduced within a week to 2 minutes 25 seconds and was maintained at that level or thereabouts for a further month. But after this time, in spite of the fact that the citric acid had been persisted in throughout, the blood coagulation time came up to 1 minute 37 seconds. In the second case exactly the same thing happened. Under the influence of the citric acid the blood coagulability diminished step by step until the coagulation time reached 2 minutes 25 seconds six weeks after the inception of the treatment. Within the next

month, in spite of the fact that the citric acid was still persisted in, the coagulability increased step by step till the coagulation time reached 55 seconds. In the third case the event was again the same. After a month's exhibition of citric acid a blood coagulation time of 2 minutes 40 seconds was re ched. Within the next fortnight the coagulation time diminished to 55 seconds and continued high from this date. The interpretation of these facts is for the present obscure. It would, however, appear from the data obtained by the measurement of the calcium salts of the blood in these cases that the decalcification of the blood which is achieved by the exhibition of citric acid is followed after an interval by an increase in the calcium salts of the blood. This last may very probably depend upon the bringing into solution again of calcium salts precipitated and eliminated from the blood by citric acid but not excreted.

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